

obtained without glycerol by taking into account both, the enzyme activity decrease and the solvent viscosity increase. Gel proteolysis kinetics is therefore diffusion limited and the diffusion is anomalous. We discuss possible explanation for these different mechanisms.

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Strain Tunes Proteolytic Degradation and Diffusive Transport in Fibrin Networks

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Proteolytic degradation of fibrin, the major structural component in blood clots, is critical both during normal wound healing and in the treatment of ischemic stroke and myocardial infarction. Fibrin-containing clots experience substantial strain due to platelet contraction, fluid shear, and mechanical stress at the wound site. However, little is understood about how mechanical forces may influence fibrin dissolution. We used video microscopy to image strained fibrin clots as they were degraded by plasmin, a major fibrinolytic enzyme. Applied strain causes up to 10-fold reduction in the rate of fibrin degradation. Analysis of our data supports a quantitative model in which the decrease in fibrin proteolysis rates with strain stems from slower transport of plasmin into the clot. We performed fluorescence recovery after photobleaching (FRAP) measurements to further probe the effect of strain on diffusive transport. We find that diffusivity perpendicular to the strain axis decreases exponentially with increasing strain, while diffusivity along the strain axis remains unchanged. Our results suggest that the properties of the fibrin network have evolved to protect mechanically loaded fibrin from degradation, consistent with its function in wound healing. The pronounced effect of strain upon diffusivity within fibrin networks offers a means of tuning the transport of proteins and other soluble factors within fibrin-based biomaterials, potentially addressing a key challenge in engineering complex tissues *in vitro*.

DNA, RNA Structure & Conformation I

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High-Bandwidth Magnetic Tweezers for Applying Torsion to Single DNA Molecules

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The mechanical and functional properties of DNA arise from its double helical structure. It is now widely accepted that the torsional properties of DNA and DNA supercoiling play an important role in the kinetics of many DNA-binding proteins, but the mechanism underlying this relationship remains unclear. To address this gap in our understanding, we need an instrument that can accurately measure and control torsional stress applied to DNA. We have developed a high-bandwidth electromagnetic trapping system that can generate a uniform magnetic field in the sample region and apply constant torque above 10^2 pN·nm on the samples under study. The octupole magnetic trap is integrated into a microscope-based particle tracking system and can rotate superparamagnetic particles with three degrees of rotational freedom. The large signal bandwidth of the current in the coils can reach above 3kHz at 800uH inductive load and the heat generated by the current is dissipated by an active PID-controlled cooling system to prevent heating biological samples. The magnetic trap is being designed to independently control force and torque, allowing us to confine superparamagnetic particles in a trap with low torsional stiffness that is suitable for torque application and measurement at biologically relevant scales. To directly measure the torsional strain in DNA, we are planning to use superparamagnetic beads coated with metal on one hemisphere. Our magnetic torque tweezers are intended to quantitatively measure the changes of torsional stress in DNA and overcome the complexity and heating problems shared by previous optical and magnetic tweezers studies.

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Enhanced Flower Relaxation of a Braided DNA Complex

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Single-polymer relaxation dynamics are key to understanding bulk-solution and intracellular rheology. Here, we investigate the effect of entanglements on polymer relaxation: we present a novel experimental system that permits entanglement of two DNA molecules by attaching them to a magnetic bead and braiding them together in a magnetic tweezer. We then actuate a relaxation event by photo-cleaving a bond that immobilizes one of the DNAs. The time course of relaxation is followed by tracking the magnetic bead position. We find that simple quasi-static models, that assume bead drag to be the dominant

dissipative effect, fail to explain the data. Instead, the data require the inclusion of a polymer dissipation term: we introduce an enhanced 'flower' model [1] that posits that relaxation is dominated by the force-induced coiling-up of the free DNA end. Our analysis places limits on the friction coefficient for the relative sliding of two interwound DNA molecules, a parameter which was somewhat inconclusively investigated in a recent study[2].

[1] Brochard-Wyart,

F. Europhysics Letters,

1995. 30(7):

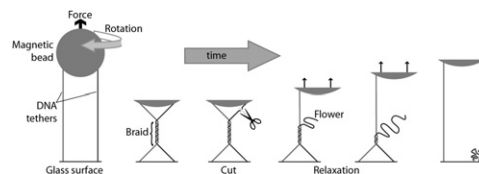
pp. 387-392.

[2] Noom, M.C., et al.

Nature Methods,

2007. 4(12): pp.1031-

1036.



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Sequence-Dependent Mechanics of DNA

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Double-stranded DNA is a semiflexible polymer that can naturally bend on length scales comparable to the size of large DNA-protein complexes like nucleosomes or protein-mediated DNA loops. The sequence of the substrate DNA does not only provide biochemical binding sites for the proteins, but also affects the local mechanical properties of the DNA. Notably, sequence can affect the intrinsic curvature of the DNA, as well as its bendability, or elasticity. While intrinsic bends in DNA and their role in protein-DNA complex formation are well studied, sequence-dependent elasticity still remains only vaguely explored. In order to separate sequence effects on elasticity from those on intrinsic curvature, we have designed sequences of DNA which have nearly identical curvatures but varied AT content and directly measured their mechanical elasticity using constant force axial optical tweezers. We found the persistence length to be highly dependent on the AT content of the DNA, differing almost thirty percent between sequences with nearly identical curvature but different sequence composition. This is a departure from conventional dinucleotide and trinucleotide models, which predict a much smaller difference between the two sequences, but consistent with estimates obtained from the crystallographic structures of protein-DNA complexes.

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Single Molecule Studies of the Effect of Spermidine on DNA Mechanics and Viral DNA Packaging

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Polyamine ions such as spermidine³⁺, along with monovalent and divalent salt ions, screen the negatively charged backbone of dsDNA and thereby facilitate processes in which DNA is confined in small spaces, such as viral DNA packaging. We use single-molecule optical tweezers assays to study Bacteriophage phi29 DNA packaging and the effect of spermidine, Mg²⁺, and Na⁺ on DNA condensation and elasticity. We determine the concentration of spermidine at which dsDNA condenses and we report a monotonic increase in stretch modulus and a monotonic decrease in persistence length at incremental spermidine concentrations up to the concentration at which dsDNA condenses. We also discuss the kinetics of spermidine binding onto dsDNA and the forces required to unravel condensed DNA.

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Triple Hydrogen Bonds in DNA Modify the Transition from Right- to Left-Handed Forms

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Double-stranded DNA usually adopts a right-handed B-form in aqueous solution, but alternative DNA conformations can also exist and play important roles in a wide range of cellular processes. For example, DNA melting (strand separation) is required to initiate DNA replication as well as transcription. Moreover, the over-production of left-handed Z-form DNA in cells is thought to be the trigger for auto-immunity in lupus. Therefore, understanding the underlying mechanics of right- to left-handed DNA transitions is very important to begin to understand how cellular processes depend on alternative DNA conformations. Two of the most influential factors related to this transition are the tension on DNA and the degree of hydrogen bonding. Magnetic Tweezers enable us to unwind single DNA molecules to investigate the dynamics of right- to left-handed DNA transitions at different tensions. Moreover, by substituting diaminopurine (DAP) deoxyribonucleotides for dATP in PCR reactions, completely triply hydrogen-bonded DNA fragments have been produced. These and normal DNA fragments